

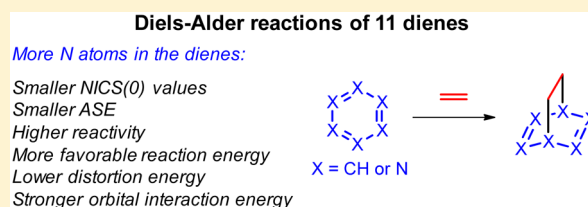
Diels–Alder Reactivities of Benzene, Pyridine, and Di-, Tri-, and Tetrazines: The Roles of Geometrical Distortions and Orbital Interactions

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S Supporting Information

ABSTRACT: The cycloadditions of benzene and ten different azabenzene (pyridine, three diazines, three triazines, and three tetrazines) with the ethylene dienophile have been explored with density functional theory (M06-2X) and analyzed with the distortion/interaction model. Activation barriers correlate closely with both distortion energies and interaction energies over an activation energy range of 45 kcal/mol. The replacement of CH with N increases Diels–Alder reactivity due not only to the more favorable orbital interaction, but also to a decrease in distortion energy. The rates of reactions are greatly influenced by the nature of the bonds being formed: two C–C bonds > one C–C bond, and one C–N bond > two C–N bonds. The activation energy of Diels–Alder reactions correlates very well with reaction energies and with the NICS(0) values of the aromatic dienes. The distortion energy of the Diels–Alder reaction transition states mostly arises from the diene out-of-plane distortion energy.



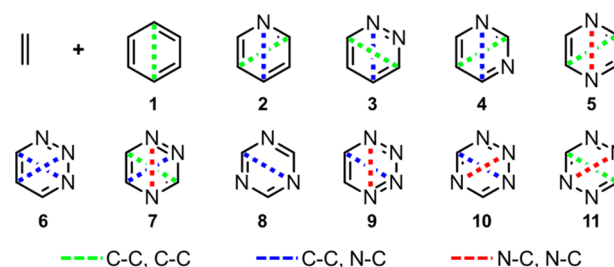
INTRODUCTION

Heteroaromatic inverse-electron-demand Diels–Alder cycloadditions have wide applications in bioorthogonal chemistry,¹ natural product synthesis,² metal–organic framework modification,³ carbon nanotube functionalization,⁴ and microarray construction.⁵ The Diels–Alder reactions of 1,2,4,5-tetrazines have been studied in detail by organic community for more than half a century.⁶ Since the first examples of using tetrazines for bioorthogonal chemistry in 2008,⁷ various tetrazines have been developed as azadienes in bioorthogonal cycloadditions.⁸ In addition, 1,2,3- and 1,2,4-triazines have been shown to be useful dienes in Diels–Alder reactions of value in organic synthesis and bioorthogonal chemistry.⁹ However, benzenes, as well as pyridines and pyridazines are usually not good dienes.¹⁰ Computational studies of these reactions also show that each additional nitrogen atom in the ring can decrease the activation barrier for cycloaddition, but there has been no complete and detailed analysis of the origins of the different reactivities. The groups of Ess and Bickelhaupt studied reactions of pyridine, 1,2-diazine, 1,2,3-triazine, and 1,2,4,5-tetrazine.¹¹ They came to the surprising conclusion that reactivity differences in the reaction are controlled by differences in closed-shell repulsion. We were also investigating these reactions at that time, and we now show that these classic inverse-electron-demand Diels–Alder reactions are not only controlled by interaction energy, which includes electrostatic interaction, closed-shell repulsion, and intermolecular charge-transfer orbital interaction, but also by distortion energy. We have performed a computational study of the origins of the reactivity of six-membered nitrogen heterocycles. We have addressed the changes in electronic

structure caused by aza substitution and how this affects cycloaddition reactivity.

The Diels–Alder reactions between ethylene and benzene plus six-membered azabenzene with 1–4 N atoms, 1–11, were explored in order to understand the reactivity changes caused by aza substitution (Scheme 1). The regioselectivity, that is

Scheme 1. Aromatic Dienes 1–11 Investigated^a



^aThe cycloaddition sites are indicated with dashed lines, and are color-coded according to whether C–C or N–C bonds are formed in the corresponding Diels–Alder reactions.

preferences for addition to form C–C or C–N bonds in products, were also studied. The roles of aromaticity and of transition state distortion and interaction energies were assessed. We find that the replacement of carbon by nitrogen reduces the σ aromaticity of the 6π systems, in part by bond localization. The substitutions also influence both distortion

Received: November 17, 2015

Published: January 23, 2016

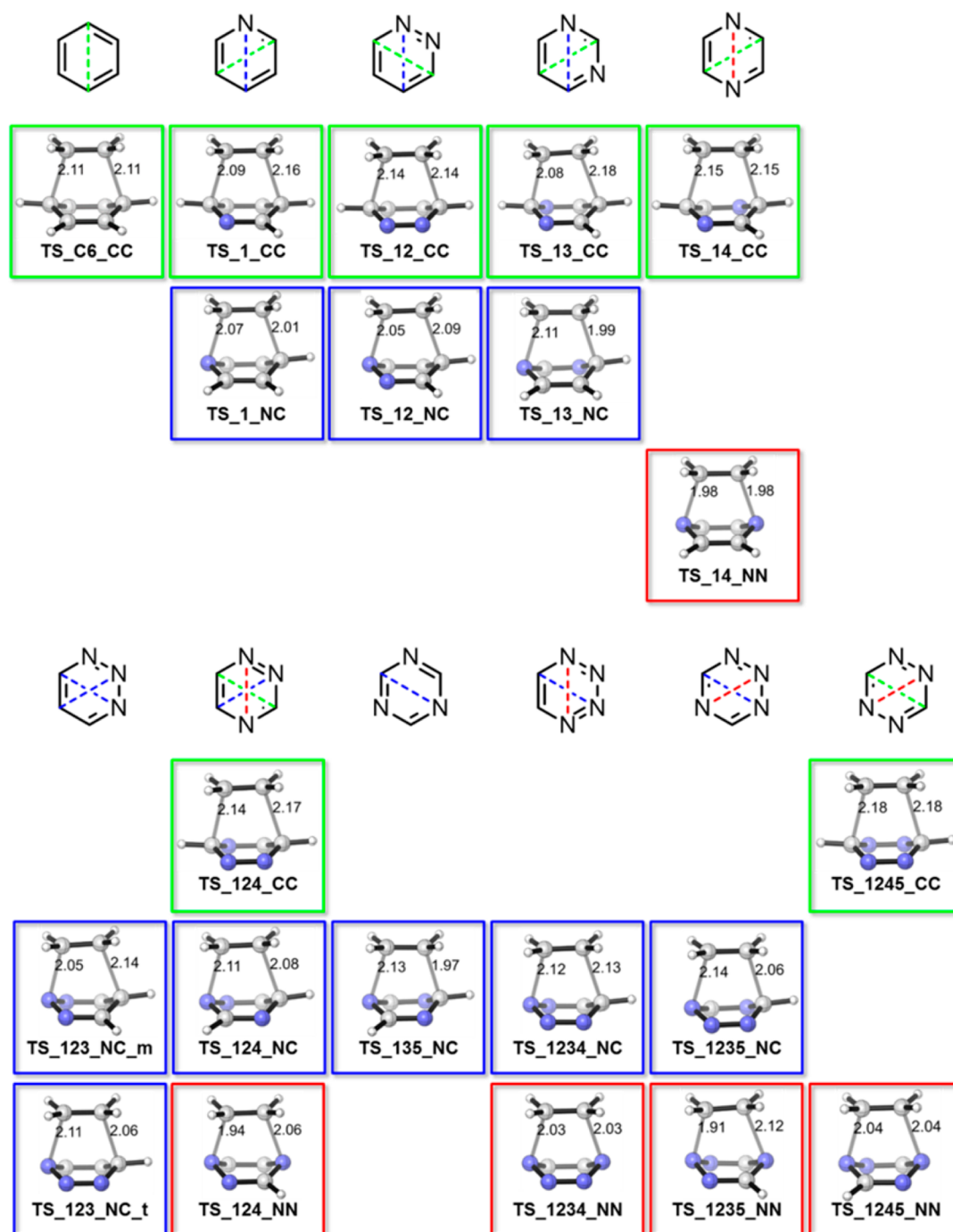


Figure 1. M06-2X/6-311+G(d,p)-optimized transition structures of the Diels–Alder reactions of aromatic dienes 1–11 with ethylene.

and interaction energies, which are very important in determining the reactivity of the aromatic compounds.

COMPUTATIONAL METHODS

All the calculations were carried out with Gaussian 09.¹² Geometry optimizations and energy calculations were performed with the M06-2X method.¹³ The 6-311+G(d,p) basis set was used for all atoms. Frequency analysis verified that the stationary points are minima or saddle points. The GIAO (gauge-including atomic orbital) calculations¹⁴ were performed at the same level. The frontier molecular orbitals (FMOs) and their energies were computed at the HF/6-311+G(d,p) level using the M06-2X/6-311+G(d,p) geometries. Computed structures are illustrated using CYLview.¹⁵

RESULTS AND DISCUSSION

Transition Structures of Diels–Alder Reactions.

Forming bond lengths and activation barriers for M06-2X/6-311+G(d,p)-optimized transition structures of the Diels–Alder reactions of aromatic dienes 1–11 with ethylene are shown in Figure 1 and Table S1 (Supporting Information). These transition structures are arranged according to the nature of the atoms that act as termini of the dienes involved in the reaction. Reactions involving the formation of two C–C bonds have earlier transition states (green boxes) than those that form one C–C bond and one N–C bond (blue boxes). Reactions that form two N–C bonds have late transition states (red boxes). Details of geometries and energies are given in Table S1.

Activation Energy Trend and Regioselectivities of Diels–Alder Reactions. The calculated activation energies $\Delta E_{\text{act}}^{\ddagger}$ corresponding to the transition structures in Figure 1 and Table S1 are graphically displayed in Figure 2. The

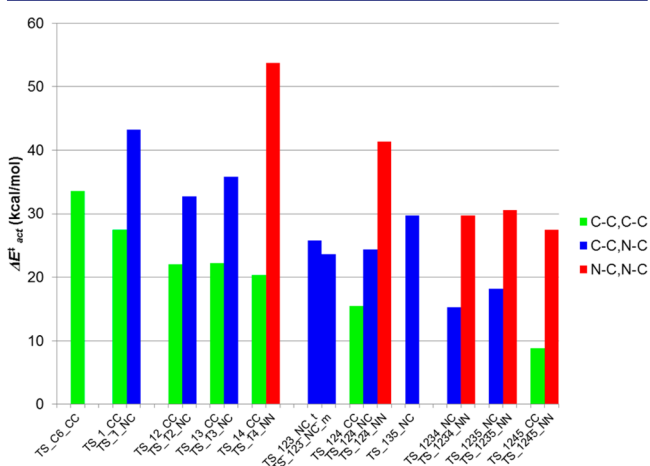


Figure 2. Activation energies $\Delta E_{\text{act}}^{\ddagger}$ (kcal/mol). Color codes are for types of new bonds formed.

activation energies for the formation of two C–C bonds (green), one C–C bond and one N–C bond (blue), and two N–C bonds (red) are color-coded. The activation barriers decrease as nitrogen atoms are added for a given type of Diels–Alder reaction.

As to the regioselectivity, the formation of two C–C bonds (green) is much more favorable than the formation of one C–C bond and one N–C bond (blue). Formation of two N–C bonds (red) has the highest barrier. Each N–C bond formation adds about 15 kcal/mol to the barrier.

Kinetic-Thermodynamic Relationship. Figure 3 is a plot of activation energy $\Delta E_{\text{act}}^{\ddagger}$ versus the reaction energy ΔE_{rxn} .

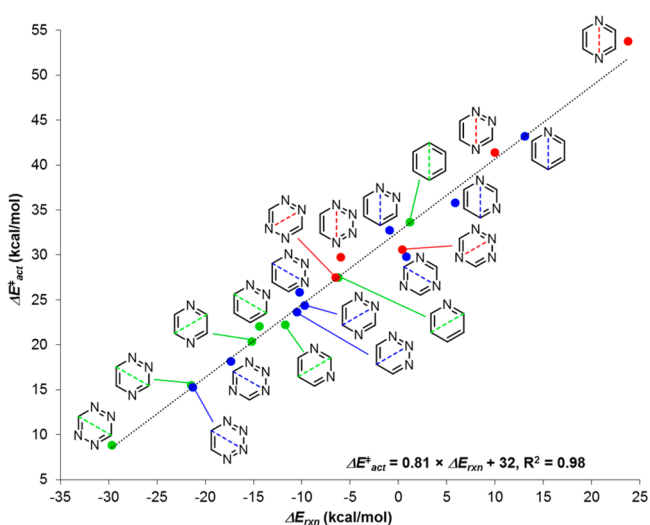


Figure 3. Plot of activation energy versus reaction energy.

There is very good linear correlation with an R^2 value of 0.98. The Dimroth relationship and its many successive others give a plot of thermodynamics with $\Delta E_{\text{act}}^{\ddagger} = 1/2 \Delta E_{\text{rxn}}$. Figure 3 shows a larger dependence of activation barrier on reaction energy.

Relationship between Activation Energy and Aromaticity of Different Dienes. The dienes 1–11 are all aromatic systems. As CH groups are replaced by nitrogens, the activation barriers for Diels–Alder reactions decrease for a given type of bond formation. We investigated whether the replacement of carbon by nitrogen reduces the aromaticity of the 6π systems, perhaps by bond localization resulting from the high electronegativity of nitrogen compared to carbon. The aromaticity of these heterocycle dienes was evaluated. The nucleus-independent chemical shift (NICS)¹⁶ is one of the popular magnetic indicators of aromaticity. NICS is the negative of the magnetic shielding. NICS(1) values (i.e., at point 1 Å above the ring center) are recommended as good measures of π effects than NICS(0) values (i.e., in ring centers).

Our NICS(1) calculations for these dienes show that the aromaticity of all the azines are like that of benzene, with NICS(1) values around -10.0 ppm and -11.0 ppm (Figure S1). This is in agreement with the work done by Schleyer's group.¹⁷ Although NICS(0) is not recommended to assess the π aromaticity, it is nevertheless a good index to evaluate the local circulations of electrons in bonds. The computed NICS(0) values range from -8.00 ppm to 0 ppm, and are a more sensitive measure of the influence of the heteroatoms. There is very good correlation between the activation energy of Diels–Alder reactions and NICS(0) values of these dienes, with R^2 equal to 0.99 (Figure 4). Benzene has the most negative NICS(0) value, and 1,2,4,5-tetrazine has a negligible NICS(0) value.

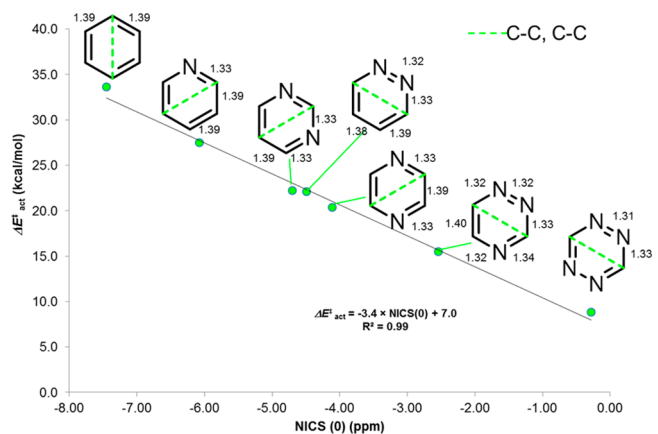


Figure 4. Plot of activation energy versus NICS(0) of aromatic dienes that undergo formation of two C–C bonds in the Diels–Alder reaction with ethylene. Bond lengths (Å) of the dienes are labeled next to the corresponding bonds.

Another common way to assess aromaticity is the aromatic stabilization energy (ASE). The ASE is an energetic criterion to evaluate aromatic stability through isodesmic and homodesmic reactions, using nonaromatic reference structures with localized single and double bonds.¹⁸ Cyclic reference compounds balance ring strain and other secondary factors and are better suited for ASE and other aromaticity evaluations.¹⁹ The isodesmic reactions of benzene and each of the azines that we used are shown in Figure 5 (eq 1). Taking 1,2,4,5-tetrazine as an example, the isodesmic reaction for computing ASE is eq 2 in Figure 5. The idea is to compare energies of delocalized aromatics to those of compounds that have localized C=C, C=N, and N=N bonds.

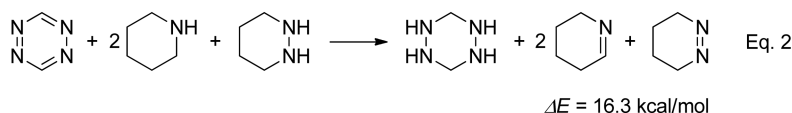
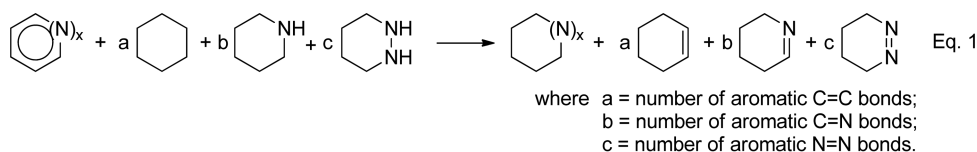


Figure 5. Isodesmic reactions to evaluate the ASE of aromatic dienes.

Figure 6 shows that the activation energy for Diels–Alder reactions of aromatic dienes correlates linearly with the ASE

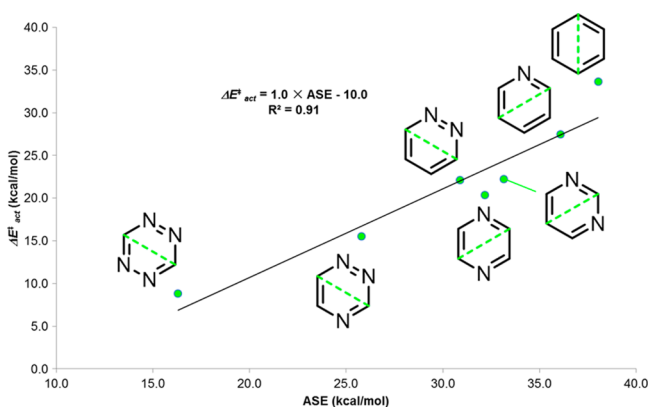


Figure 6. Plot of activation energy versus aromatic stabilization energy for reactions involving formation of two C—C bonds.

value, in accordance with the NICS(0) value. In the case of formation of two C—C bonds in the reaction, the slope is just 1.0. That is, a reduction in ASE is the same as the reduction in activation energy.

Distortion/Interaction Model Analysis. Figure 7 shows a potential energy surface along some reaction coordinate, and

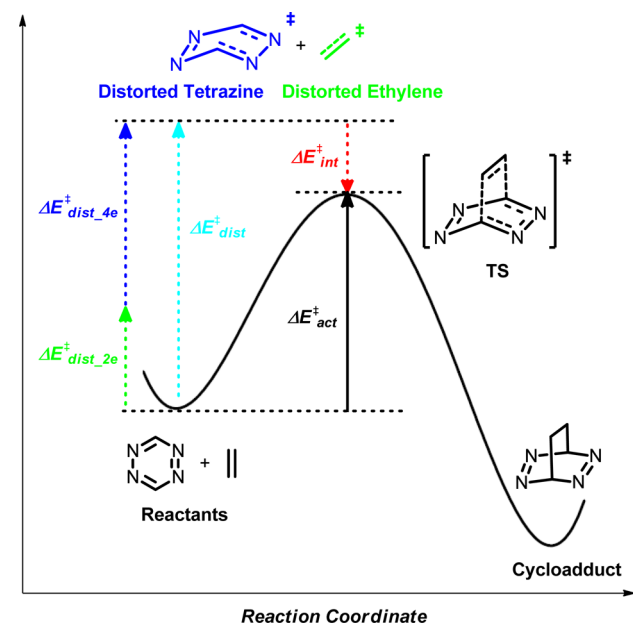


Figure 7. Distortion/interaction model.

also defines the distortion/interaction model,²⁰ also known as the activation strain model.^{21,22} The activation energy $\Delta E_{\text{act}}^{\ddagger}$ of the reaction is decomposed into the distortion energy of the reactants plus the interaction energy $\Delta E_{\text{int}}^{\ddagger}$ between the distorted reactants at the transition geometry ($\Delta E_{\text{act}}^{\ddagger} = \Delta E_{\text{dist}}^{\ddagger} + \Delta E_{\text{int}}^{\ddagger}$). The distortion energy $\Delta E_{\text{dist}}^{\ddagger}$ is composed of the distortion energies of diene ($\Delta E_{\text{dist}_4e}^{\ddagger}$) and dienophile ($\Delta E_{\text{dist}_2e}^{\ddagger}$) to achieve the transition state geometry.

The activation, distortion, and interaction energies for the 21 Diels–Alder reactions with ethylene involving 11 different aromatic dienes were computed. The plots of these activation energies versus total distortion energies and interaction energies are shown in Figures 8, parts a and b, respectively. The activation energies correlate very well with the distortion energies, with R^2 equal to 0.98. The activation energies increase as the distortion energies increase, and the distortion energies range from 22 to 53 kcal/mol. The correlation between activation energies and interaction energies is reasonably good; the interaction energies range from -13 kcal/mol (stabilizing) to 1 kcal/mol.

The interaction energy between the distorted dienes and dienophiles at the transition geometry is composed of a variety of energetic terms, such as electrostatic interaction, closed-shell (Pauli) repulsion, and intermolecular occupied-to-vacant orbital interaction (also termed charge-transfer energy).²³ An interaction energy dissection analysis was performed for some of these reactions by the groups of Ess and Bickelhaupt.¹¹ The electrostatic interaction is around -50 kcal/mol; the orbital interaction is around -55 kcal/mol; and the Pauli repulsion is generally above 90 kcal/mol, up to 114 kcal/mol. All these energy terms are very large numbers, and they mostly cancel out each other. The net interaction is a relatively small number. We have calculated a very small range from -13 to 1 kcal/mol for interaction energy. The evaluation of the contributions of these different interaction energy terms is an ongoing challenge, and many energy decomposition analysis (EDA) methods²⁴ are still being developed.

Our calculations are in agreement with previous calculations and experiments that show high regioselectivity, favoring C—C bond formation over N—C bond formation.²⁵ This arises from the efficient orbital overlap between the p orbitals of two carbon atoms. The interacting π orbital on the more electronegative nitrogen atom is more contracted and is less favorable for orbital overlap, as reflected also in the weakness of a C—N bond compared to a C—C bond.

Both distortion energies of diene and dienophile contribute to the distortion energy of the Diels–Alder transition-state structure. The distortion energy of the dienes range from 16 to 38 kcal/mol, and the distortion energy of the dienophiles range from 5 to 15 kcal/mol (Figure 9). The main contribution to the

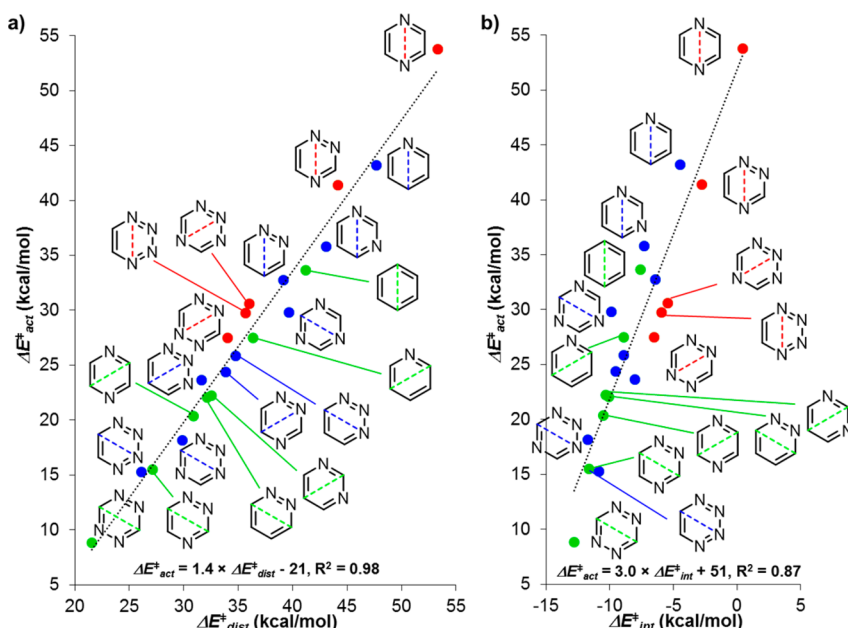


Figure 8. Plots of activation energy versus a) total distortion energy or b) interaction energy. The data points are color-coded according to the number of C–N bonds formed in the reactions, indicated by the structures shown next to them.

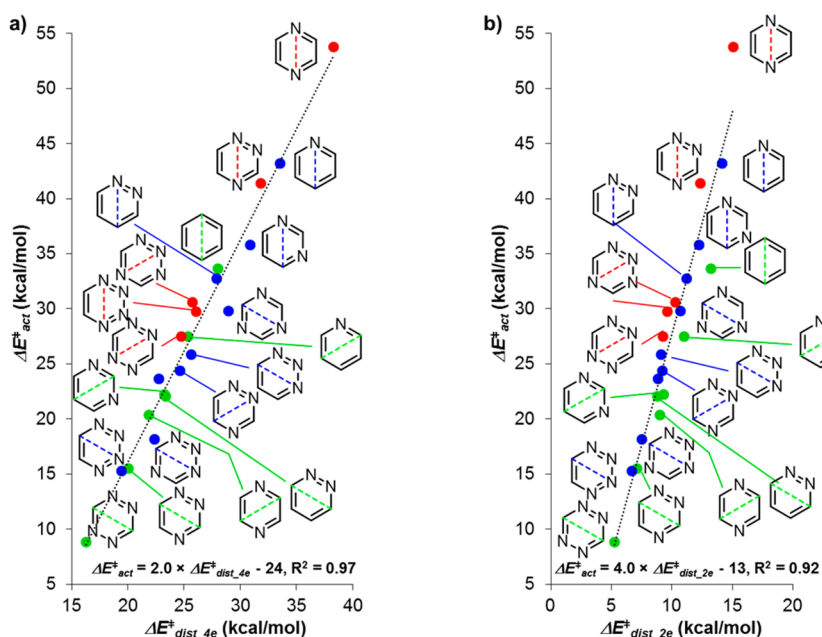


Figure 9. Plots of activation energy versus a) distortion energy of diene or b) distortion energy of dienophile. The data points are color-coded according to the number of N–C bonds formed in the reactions, indicated by the structures shown next to them.

total distortion energy comes from the distortion energy of the aromatic diene, which is larger than the out-of-plane CH bending of ethylene in the transition state.

In the Diels–Alder transition structures, the bond stretching, bond angle bending, and dihedral angle distortion contribute to the distortion of the diene or dienophile. The prominent distortion in the transition state comes from the out-of-plane bending dihedral angle ω of dienes, shown in Figure 10. In both benzene and 1,2,4,5-tetrazine planar ground-states, the out-of-plane bending dihedral angle ω is 0° . The angular distortion energy, $\Delta E_{\text{dist},\omega}$ is the energy difference between optimized structure with fixed dihedral angles and the planar ground-state structure. The out-of-plane bending dihedral angle ω becomes

17° and 16° for benzene and 1,2,4,5-tetrazine transition-state structures, respectively. The corresponding angular distortion energy, $\Delta E_{\text{dist},\omega}$ is 20.9 and 10.8 kcal/mol, for benzene and 1,2,4,5-tetrazine, respectively. This angular distortion energy constitutes 75% and 66% of the total diene distortion energies of the transition states (28.0 and 16.3 kcal/mol, respectively). To compare the ease of distortion of benzene and 1,2,4,5-tetrazine, a scan of the out-of-plane dihedral angle ω starting from 0° to 20° , in interval of 2.5° , was performed. Figure 10 shows the plot of $\Delta E_{\text{dist},\omega}$ versus the out-of-plane bending dihedral angle ω . 1,2,4,5-Tetrazine is easier to distort than benzene, consistent with the previous discussion of the different aromaticities of dienes. As shown in Figure 4, aromaticity

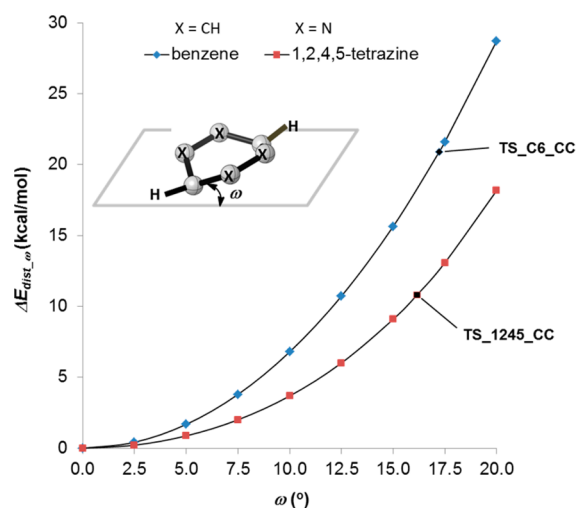


Figure 10. Plot of $\Delta E_{\text{dist},\omega}^{\ddagger}$ versus the out-of-plane dihedral angle ω for benzene and 1,2,4,5-tetrazine.

becomes weaker as more N atoms are included, leading to lower distortion energies.

In addition to the single-point analysis at the transition-state structures, we have also carried out the distortion/interaction analysis along the reaction coordinate for benzene and 1,2,4,5-tetrazine. As shown in Figure 11, the total energies for 1,2,4,5-tetrazine Diels–Alder reaction are always lower than those of benzene. Both the lower distortion and more favorable interaction contribute to the lower barrier of 1,2,4,5-tetrazine Diels–Alder reaction. The transition state is the point whose upward slope of distortion energy equals the downward slope of the interaction energy. All along the reaction coordinate, the distortion energies and interaction energies are more favorable, the result of lower bending energy and lower LUMO energies for 1,2,4,5-tetrazine.

The Diels–Alder reactivities increase from benzene through tetrazines. 1,2,4,5-Tetrazine has the highest reactivity. This is due to its smallest distortion, especially the smallest out-of-plane bending dihedral angle distortion. Ess and Bickelhaupt attributed the change in activation energies to change in closed-shell repulsion,¹¹ but the change in distortion energies,

especially the out-of-plane bending distortion energies, also contribute to the change in activation energies.

CONCLUSIONS

The computational studies of cycloadditions of benzene through tetrazines have revealed the origins of their different reactivities. There are excellent linear correlations of activation barriers with both distortion energies and interaction energies. The nitrogen substitution causes higher Diels–Alder reactivity of azadienes. It is not only due to the more favorable interaction, but also the less distortion energy. The out-of-plane bending dihedral angle distortions of these aromatic dienes make a major contribution to the distortion energy of the Diels–Alder transition states. This can be attributed to the σ aromaticity of dienes: the nitrogen substitution cause electron localization and reduce the σ aromaticity. The understanding of how distortion and interaction energies influence reactivity will be helpful in guiding design of useful aromatic dienes in many areas of chemistry and biology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12054.

Cartesian coordinates and energies of all structures reported here. Plot of activation energy versus NICS(1) of aromatic dienes, lowest vacant orbitals of aromatic dienes, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation of the U.S.A. (CHE-1361104) for financial support. Calculations were performed on the Hoffman2 cluster at UCLA and the Extreme

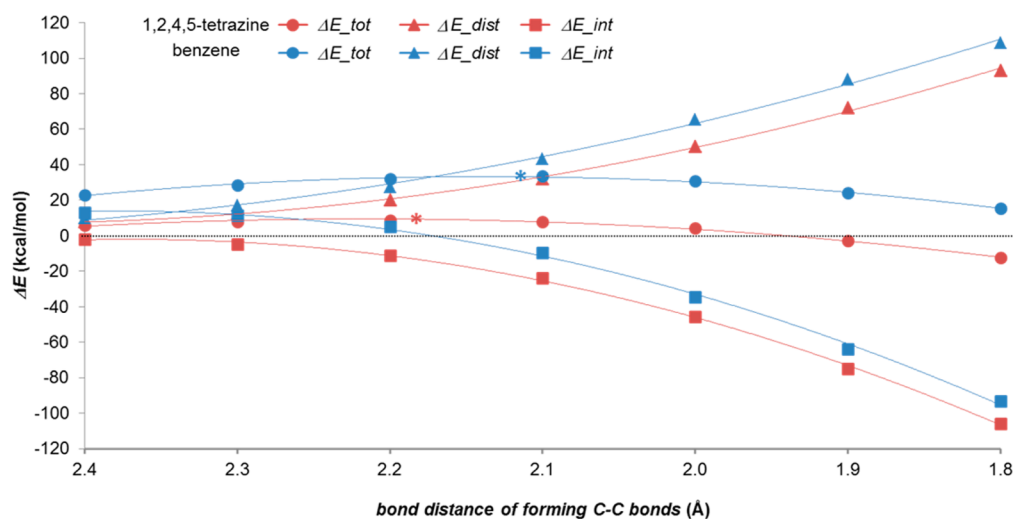


Figure 11. Plots of total energy, distortion energy, and interaction energy versus bond distance of forming C—C bonds for both benzene and 1,2,4,5-tetrazine Diels–Alder reactions. The transition states are marked with *.

Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (OCI-1053575).

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